HIV-related Cardiovascular Disease: Any role for High-density Lipoproteins?

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Abstract

The introduction of antiretroviral therapy (ART) has improved the life expectancy of patients infected with human immunodeficiency virus (HIV). However, this population is at an increased risk for non-communicable diseases, including atherosclerotic cardiovascular disease (CVD). Both ART and viral infection may be potential contributors to the pathophysiology of HIV-related CVD. The mechanisms behind this remain unclear but it is critical to delineate early biomarkers of cardiovascular risk in the HIV population. In this review, we postulate that potential biomarkers could include alterations to high-density lipoprotein (HDL). Indeed, recent data suggest that HIV and ART may induce structural changes of HDL, thus resulting in shifts in HDL subclass distribution and HDL functionality.

Introduction

The majority (>80%) of deaths due to cardiovascular disease (CVD) occurs in low- and middle-income countries (69). In sub-Saharan Africa (SSA), although communicable diseases remain the leading cause of death, the prevalence of CVD continues to increase (31). The growing burden of preventable CVD in Africa can, at least in part, be attributed to globalization, rapid urbanization and population growth over the last 30 years (44). Throughout the countries in this region, there is a growing body of evidence suggesting that the increased incidence of CVDs may also result as a consequence of communicable diseases such as HIV and tuberculosis (60).

Over 37.9 million people live with HIV worldwide, and approximately two-thirds of those people reside in SSA (70). There is still no cure or an effective vaccine, however, there have been major advances in HIV management. Indeed, antiretroviral therapy (ART) has altered the course of the epidemic, making the once-fatal disease, a chronic and more manageable condition. HIV-infected patients with access to ART can now expect improved life expectancy (53). However, this longevity can result in clinical challenges for these patients, including an increased risk of non-communicable diseases, such as CVD (61). The pathophysiological mechanisms behind this remain unclear (43, 73) but potential contributors to the aetiology of HIV-related CVD include HIV itself and the side effects of antiretroviral therapy (ART). Associated pathophysiological factors include dyslipidaemia, inflammation, immune/autoimmune activation, insulin resistance, endothelial injury and dysfunctional coagulation (19, 29, 33, 34, 66). These features, along with traditional and SSA-specific risk

factors, including diabetes mellitus and tuberculosis, respectively, may contribute to the increased risk of CVD (50, 64, 67).

Dyslipidaemia, characterised by lower high-density lipoprotein (HDL) cholesterol and raised low-density lipoprotein (LDL) cholesterol, is a prominent risk factor for CVD, and it is more common in HIV-infected individuals than in the general population (11, 21, 26, 39, 74). Lipoproteins, such as HDL and LDL, can be separated into distinct subclasses based on size, density, electrophoretic mobility, protein and lipid composition (3). Small-dense LDL is more pro-atherogenic than other LDL subfractions, most likely as a result of its better ability to penetrate the arterial wall and its increased susceptibility to modifications due to its longer circulation time compared to larger LDL (32).With regards to HDL particles, there is now mounting evidence that HDL particles may change in composition thus resulting in a shift of HDL subclasses (and function) in the presence of different cardiovascular risk factors (72). It is, therefore, appropriate to consider whether measurements of HDL function and subclass, as opposed to HDL-cholesterol concentrations, may prove to be more pertinent when assessing CVD risk.

In this review, we consider the current rise of CVD-related complications following HIV-infection/ART and highlight the need for early detection of CVD in the affected populations. We also discuss how alterations in the lipid profile of patients, specifically in HDL function and subclass, could potentially be regarded as a useful early biomarker of HIV-related CVD. We are mindful that there is accumulating evidence for both LDL and HDL subclasses as possible biomarkers for CVD prediction but the focus of this mini-review will restricted to HDL particles.

HIV and CVD

Although the pathophysiological mechanisms behind the increased risk of CVD in the HIV infected population remain unclear, the aetiology most likely relies on the combination of classic CVD risk factors, HIV itself and the metabolic side-effects of ART (73). The general population, irrespective of HIV infection status, has a substantial burden of CVD risk factors (64). HIV itself determines a state of chronic inflammation, immune activation, metabolic abnormalities and vascular dysfunction (5). In this regard, persistent inflammation and immune activation may be the most significant contributors to increased CVD risk. HIV-

infected individuals have increased concentrations of markers of monocyte activation and relatively higher levels of nonclassical (CD14-CD16+) monocytes (62, 63). Chronic inflammation and immune activation alter how lipids are processed/transported and it exacerbates structural modifications to these lipids via reactive oxygen species or the activation of enzymes such as lipoprotein-associated phospholipase A2 (22). Before the roll out of effective ART, many patients experienced dyslipidaemia related to the inflammation associated with acute infection. The typical ART-naïve lipid profile displays increased triglycerides and decreased total cholesterol, LDL- and HDL-cholesterol (17). An increase in circulating LDL together with an increase in macrophage activity increases the likelihood of oxidised-LDL (ox-LDL) formation, thus promoting foam cell accumulation (46). Additionally, the presence of chronic co-infections common to HIV-infected people, such as the Hepatitis C virus, herpes family viruses and chronic kidney disease may contribute to increased inflammation and CVD risk (49).

There is an on-going debate regarding the relative contributions of viral factors versus ART side-effects to the development of CVD in people living with HIV (4, 67). The Strategies for Management of Anti-Retroviral Study (SMART study) reported that patients assigned to discontinued ART exhibited an increased risk for CVD compared to those exposed to ART drugs (15). Since then, it has been suggested that viral infection increases the risk of CVD even in patients with complete viral suppression following ART treatment (5). However, to further complicate the matter, the risk profiles may vary function to the antiviral drug (14). Protease inhibitors (PIs), including stavudine and zidovudine, were the first antiretroviral drugs associated with increased CVD risk: their introduction into a clinical setting coincided with the first reported cases of ischaemic heart disease in HIV patients (30). Increased CVD risk was also associated with treatment with non-nucleoside-reverse transcriptase inhibitors (NNRTIs) such as efavirenz (4). The Data Collection on Adverse Events of Anti-HIV Drugs Study (DAD study) confirmed the relationship between ART and CVD, reporting a significantly increased occurrence of acute myocardial infarction, with an increased risk of 26% after 6 years of treatment with both PIs and NNRTIs (21). The harmful side effects of these older regimes include dyslipidaemia, altered glucose metabolism and have been associated with increased carotid intima-media thickness (cIMT), a common marker for subclinical atherosclerosis (24). Patients on ART, often present with low grade chronic inflammation along with raised levels of total cholesterol and LDL-cholesterol (17). ART-associated lipid abnormalities are most evident in PI-based treatment, an effect which may be

explained by its direct effect on the liver. NRTIs also have deleterious effects, usually over a longer period of time. Their mechanisms of inducing lipid abnormalities are likely related to impaired adipose tissue function and resulting dyslipidaemia (37). Dyslipidaemia is more frequent in individuals with impaired fasting glucose or diabetes mellitus than those with normoglycemia (33). HIV patients have high rates of insulin resistance. Although the rates are dropping with the improvement of ART, it is still a major concern (2). Most PIs as well as some NNRTIs, such as efavirenz, have been associated with insulin resistance and impaired secretion, thus favouring diabetes. Older generations of ART have also been associated with a specific type of body fat redistribution known as HIV-associated lipodystrophy (37). Newer ART regimes are generally better tolerated with fewer side effects directly linked to treatment, however cardiovascular and metabolic complications are still being reported (58). A recent three-year prospective study showed ART mitigated a significant increase in cIMT compared to untreated HIV- infected patients and HIV-negative patients. These findings support the argument that HIV itself, rather than the side effects of ART, is the major cause of increased CVD risk in HIV-infected patients (38).

Statins (3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase enzyme inhibitors) are the current gold standard for treating hypercholesterolemia. They are the preferred agents for reducing risk of CVD among HIV infected populations based on guidelines extrapolated from the general population (45). Many studies have reported that statins lower LDL and ox-LDL in HIV infected patients via multiple mechanisms including the downregulation of inflammatory biomarkers and improving endothelial function, thus slowing down the progression of atherosclerosis (6, 40). Despite this, statins are still underutilized and under-dosed in this population possibly due to varying reasons including concerns for drug-drug interactions, non-adherence and poor access to health care (45). The ongoing Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE; launched in 2015) is a promising clinical trial with plans to test the ability of statin medication (pitavastatin) in decreasing the risk of HIV-related CVD (28). Treatment with newer statins, together with the implementation of lifestyle modifications and switching to newer ART should help lower the risk of CVD in HIV infected populations.

HIV-related CVD in SSA

Data regarding the increased risk of CVD in the HIV-infected population are mainly taken from high-income countries and it is not clear if the results from these countries can be translated in the African context. The HIV-positive population in North America and Western Europe mainly consists of men while in SSA, the HIV-positive population mainly consists of women (65). Recent data also suggest that in SSA, people living with HIV tend to have fewer classical CVD risk factors compared to the general population (9, 68). Furthermore, most of the research from high-income countries has focused on a subtype of HIV that is not predominant in Africa. HIV-1, group M, subtype C makes up 55 to 60% of all HIV-1 infections and is the predominant subtype of HIV found in SSA, however, the majority of research has been performed on Caucasian populations with HIV-1, subtype B (42). The two subtypes differ as much as 30% in their genome (51). Therefore, we cannot exclude that subtype C, HIV infections may have a slightly altered pathophysiology of HIV-related CVD (and HDL function and quantity) in comparison to subtype B infections. In 2016, South Africa implemented the test-and-treat policy as the world's largest ART program which is subsidized by the government (60). Although the majority of South Africa's HIV-infected population is receiving ART, the lack of resources in many other developing nations in Africa results in far fewer patients being ART-treated. When studying HIV-related CVD, one should therefore consider separating the population into treated versus untreated groups and consider the type of treatment (14, 42). The pathophysiology of HIV-related CVD in SSA may also differ from the rest of the world due to a high prevalence of tuberculosis co-infection, socioeconomic differences and variances in ethnic susceptibility to coronary artery disease (67) (see figure 1). More specifically, a healthy population of African descent presents with different lipid profiles, HDL subclasses and functions compared to Caucasians (71).

CVD, HDL function and subclass

HDL is the smallest (8-12nm in diameter) and most dense (> 1.21 g/ml) of all lipoproteins (41). HDL acts mainly to remove and transport cholesterol from peripheral tissues and cells to the liver for excretion in bile and faeces (25). This anti-atherogenic process is known as reverse cholesterol transport (RCT) and is mediated through the ATP-binding cassette (ABC) A1 and ABCG1 transporters (52). It was therefore assumed that pharmacologically increasing HDL-cholesterol should theoretically decrease the risk of CVD. However, the results from recent, large-scale clinical trials have proved this therapeutic strategy to be

ineffective (7, 57). Recent literature suggests that changes in HDL function and subclass distribution may, in fact, more accurately represent an individual's risk of CVD (54, 56).

Beyond its role in RCT, HDL performs other cholesterol-independent physiological functions including anti-inflammatory, anti-thrombotic, antioxidant, and anti-apoptotic functions (20, 48). HDL is the most heterogeneous lipoprotein class as it varies widely in size, density, electrophoretic mobility, protein and lipid composition. Agarose gel electrophoresis can be used to separate HDL into different subclasses (3). New, more accurate methods for the quantification of subclasses are now available, including the Lipoprint system (Quantimetrix, Redondo Beach, CA) which denotes HDL subclasses as large, intermediate and small subclasses (18). Adding to the complexity, is the ability of each HDL subclass to perform different functions at differing efficacies. Indeed, epidemiological studies suggest that decreased levels of large HDL are associated with increased CVD risk (16, 36). Conversely, preclinical studies suggest that small HDL is structurally associated with cardioprotective enzymes, apolipoproteins and lipids such as sphingosine-1-phosphate (S1P) (8, 13, 72). The diverse roles played by HDL, make the measurement of HDL function and subclass distribution attractive potential biomarkers for CVD risk assessment.

HDL & HIV

One of the principal drivers for the increased CVD risk in both ART naïve and treated HIV-infected patients is dyslipidaemia (17, 21). A large cross-sectional study conducted in South Africa reported that 90% and 85% of the ART-naïve and ART-treated participants presented with dyslipidaemia, with low HDL-C being the most common lipid abnormality. Furthermore, dyslipidaemia was also associated with abnormal glucose metabolism in both ART-naïve and treated participants (12).

In addition to its reduced quantity, the beneficial effects of HDL can also be altered and become dysfunctional. The HIV protein, Nef, impairs ABCA-1-dependent cholesterol efflux from human macrophages (46), whilst ART improves cholesterol efflux capacity but not to a level similar to that of healthy individuals (63). Nef has also been shown to cause dyslipidaemia and the formation of foam cells in mouse models of atherosclerosis (10). HIV infection favours the redirection of cholesterol to apolipoprotein B lipoproteins which may precipitate atherogenesis (55). HIV-infected patients have reduced paraoxonase (PON) activity (an antioxidant enzyme which forms part of HDL particles) compared to uninfected

controls (59). Similarly, systemic inflammation lowers the anti-inflammatory effect of HDL and it may transform into a dysfunctional and pro-inflammatory particle (35). Dysfunctional HDL in virally suppressed HIV-infected individuals may potentiate atherosclerosis by promoting monocyte-derived foam cell formation (1). Dysfunctional HDL has downstream consequences that are specific to CVD, which potentially makes it an attractive, early biomarker compared to inflammatory markers which are non-specific (36). Furthermore, HIV has also been associated with the expression of several microRNAs involved in lipid metabolism (38). All these findings support the shift in HDL function associated with HIV infection.

Only a few studies have explored the associations between HIV infection and HDL subclass. American and European HIV-infected patients have larger HDL particles that are less stable and less receptor competent compared to healthy controls (23, 27). These results suggest that similar to other cardiovascular risk factors, HIV infection causes shifts in HDL subclass distribution. Munger et al, examined the lipid profile and particle size of ART-treated patients with traditionally normal lipid profiles and found decreased large HDL, increased small LDL and reduced reverse cholesterol efflux (47). Recently, our group observed alterations in HDL subclass in a population of HIV-infected individuals in South Africa with higher distributions of larger HDL subclasses detected in HIV-infected individuals compared to healthy patients (62). A detailed characterisation of HDL subclass and function in HIV patients treated with/without ART would be of great interest to evaluate the effect of HIV versus ART as a cardiovascular risk factor.

Conclusion

There is clear evidence in the literature showing that HIV-positive individuals treated with ART have a greater risk of developing CVD at an accelerated rate compared to the general population, due to a net pro-atherogenic environment affecting chronic inflammation and immune activation. Clinical trial data suggest that the quality of HDL, rather than the quantity, may be considered to comprehensively define the risk for CVD. One of the possible mechanisms by which HIV and ART favour CVD might be by adversely altering HDL subclass distribution, composition and functionality (Figure 2). Studies that fully characterise their impact may identify key components of HDL that could be explored as early biomarkers of cardiovascular risk in HIV-infected patients.

Disclosures

None declared by the authors

Contributions

PH assimilated and compiled the final manuscript which was written in part by SL, NW, FK, HS, and MF. All authors contributed equally in review of the final manuscript.

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Figure Legends

Figure 1: Proposed pathophysiology of HIV-related CVD in sub-Saharan Africa (SSA).

Figure 2. Proposed mechanism depicting how HIV and ART increase the risk for CVD. We suggest that both the HIV viral infection and ART can potentially alter HDL subclass and function, thus increasing the risk for CVD.

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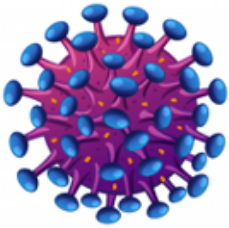


HIV infection

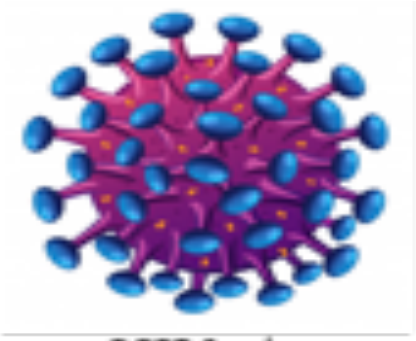
Classic and SSA-specific risk factors

Antiretroviral therapy

Persistent inflammation and immune activation

Dyslipidemia
Lipodystrophy
Insulin resistance
Endothelial injury
Dysfunctional coagulation

Increased risk for CVD



HIV virus

Antiretroviral therapy

Shift in HDL subclass distribution

Small HDL → Large HDL

Decreased HDL functionality

Reduced:

Reverse cholesterol efflux

Anti-oxidative function

Anti-apoptotic function

Anti-inflammatory function

Anti-thrombotic function

Increased cardiovascular disease risk